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C2C CAA CLH CNG C1672 C215 C247 C25Y C253 C29Y C292 C30Y C32Y C321 C36Y C360 C362 C364 C43X C610 C623 C624 C630 C634 C67D C672 C69Y C774 C80Y C802
U1S S1313 S1345

(56) Documents cited
EP 0186685 A
JP 87/59294 A
J.Chem. Soc. Chem. Comm. 459-60 (1986)

(58) Field of search
UK CL (Edition J) C2C CLH

(54) 3, 4–diamino–tetrahydropyran–pt (II)

(57) This Invention relates to novel substituted (3, 4–diaminotetrahydropyran) dihaloplatinum – (II) complexes and processes of preparation therefor. These compounds may be used at catalysts and, as well have, anticancer properties.

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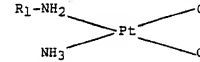
Cis-Platinum Derivatives

This invention relates in one aspect to new platinum diamine compounds; in a further aspect, this invention relates to processes of preparing such compounds. Still further, this invention also provides a method of using such diamine compounds for medical purposes; the invention also provides compositions containing, as the active ingredient, platinum diamine derivatives as defined hereinafter.

Known platinum diamine compounds are described by Rosenberg (B. Rosenberg et al, Nature 222 385 (1969). Specifically, cis-dichlorodiamineplatinum(II), also known as cisplatin, as described, discloses both cis- and trans-isomers and are disclosed to exist in an aqueous solution in the 2+ oxidation state. In addition, octahedral 4+ analogs are also known.

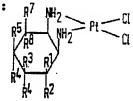
Cisplatin compounds of the formula

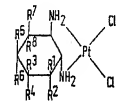


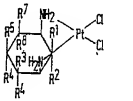
(I),

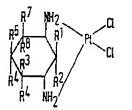
wherein R_1 is a cyclic ring containing between 3 to 8 carbon atoms, are disclosed in Braddock et al, Chem.-Biol. Interact., 1975, 11(13), 145-161. These compounds have relatively little activity for medicinal purposes (as discussed hereinafter).

Japanese Patent: Application No. Sho 60-127551, Dated: June 12, 1985 discloses compounds of the following formulae:



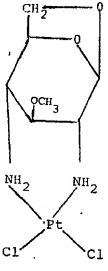






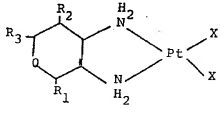
In the above compounds, groups R^1 through R^8 are designated as hydrogen or hydroxy, with the proviso that one carbon atom in the cyclohexane ring cannot be substituted by two OH groups. Such compounds are stated to have certain medicinal activity.

Another publication is J. Chem. Soc., 1986, page 459 which discloses two diamino sugars, namely, the platinum complexes of methyl 2,3-diamino-2,3-dideoxy-D-mannopyranoside, and 2,3-diamino-2,3-dideoxy-D-glucose. European application 167,071 of January 8, 1986 discloses compounds of the formula



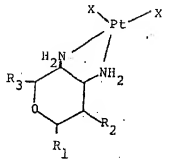
US Patent No. 4,587,331 patented May 6, 1986 by J.J. Hlavka et al discloses other platinum complexes of a linear and cyclic nature, in which the platinum may have dihydroxy substituents.

The present invention provides new derivatives of cis-platinum compounds having the formula



(II)

or the corresponding positional isomer of the formula



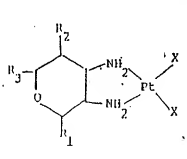
(III)

wherein X is a protective group, (to be described hereinafter) R_1 is H, alkyl,or O-alkyl, R_2 is H, OH, alkyl, or O-alkyl and R_3 is H, alkyl or alkyl-alkoxy. Each of the isomers (II) and (III) exist as cis and trans stereo-isomers. For convenience, these isomers will be generally called "cis-platinum compounds and their corresponding positional isomers."

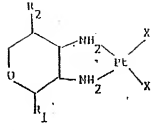
Protective group X may be any suitable group such as, a halogen, e.g., chlorine, bromine, or iodine, a nitrate, sulfate and the anion of a monobasic organic acid such as glucuronic acid; or still further, X can be a monodentate ligand or a di-anionic chelate group, e.g. oxalates ($C_2O_4^{2-}$), malonates, $[(O_2C)_2CR'R"]$ (wherein R' and R" are H, alkyl, OH, or taken together represent alkylene units of 2-3 carbons in length) which are typical examples of 0,0-bonded chelates or 1,1-cyclobutane dicarboxylates.

Thus, in one aspect, the present invention provides a compound selected from the group consisting of

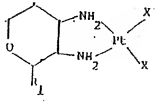
(a)



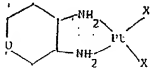
(b)



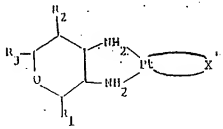
(c)



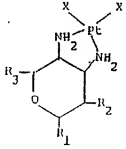
(d)

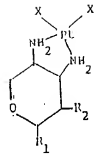


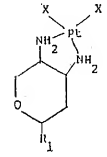
(e)

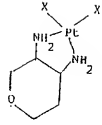


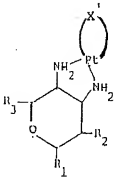
(f)



(g)  ;

(h)  ;

(i)  ; and

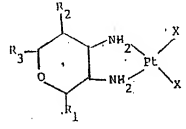
(j) 

wherein X is a protective group, selected from the group consisting of halides and di-anionic chelating agents, R_1 is H, alkyl or O-alkyl, R_2 is H, OH, alkyl or O-alkyl, and R_3 is H, alkyl, or alkylalkoxy.

The novel compounds of the present invention may find application as chiral catalysts and as intermediates for chemical catalysts useful for asymmetric synthesis of different compounds. In addition, such compounds can have anti-microbial activity. Still further, such compounds find use as anti-cancer compounds, as described herein in greater detail.

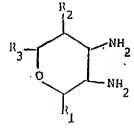
This invention also relates to a process of preparing such compounds, which process is selected from one of the following:

(a) a compound of the formula



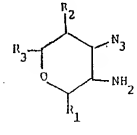
which comprises:

(i) reacting a compound of formula

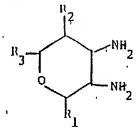


with K_2PtX_4, or

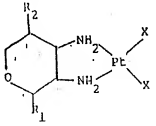
ii) first catalytically reducing a compound of formula



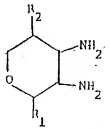
to form a compound of formula



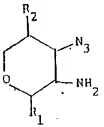
and then reacting that compound with K_2PtX_4;
or (b) a compound of the formula



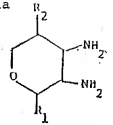
which comprises
(i) reacting a compound of formula



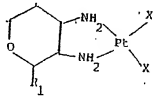
with K_2PtX_4, or
(ii) first catalytically reducing a compound of formula



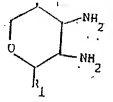
to provide a compound of formula



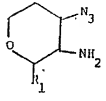
and then reacting that compound with K_2PtX_4;
or (c) a compound of the formula



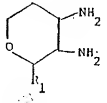
which comprises:
(i) reacting a compound of formula



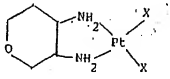
with K_2PtX_4, or
(ii) first catalytically reducing a compound of formula



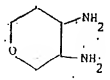
to provide a compound of formula



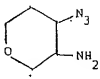
and then reacting that compound with K_2PtX_4;
or (d) a parent compound of the formula



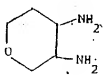
which comprises:
(i) reacting a compound of formula



with K_2PtX_4, or
(ii) first catalytically reducing a compound of formula

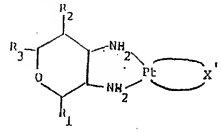


to a compound of formula



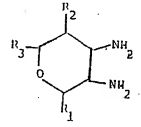
and then reacting that compound with K_2PtX_4;

or (e) an analog compound of the formula

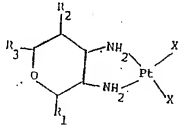


which comprises:

(i) reacting a compound of formula

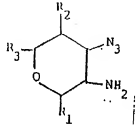


with K_2PtX_4 to provide a compound of formula

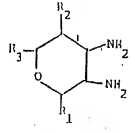


then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion, X'; or

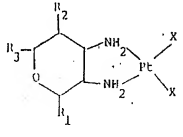
(ii) first catalytically reducing a compound of formula



to form a compound of formula

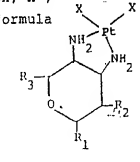


then reacting that compound with K_2PtX_4 to provide a compound of formula



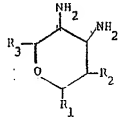
and then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion, X';

or f) a compound of the formula



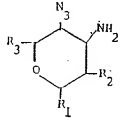
which comprises:

(i) reacting a compound of formula

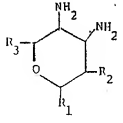


with K_2PtX_4, or

(ii) first catalytically reducing a compound of formula

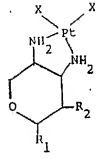


to form a compound of formula



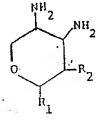
and then reacting that compound with K_2PtX_4;

or (g) a compound of the formula



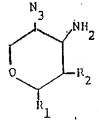
which comprises:

(i) reacting a compound of formula

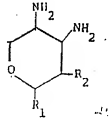


with K_2PtX_4, or

(ii) first catalytically reducing a compound of formula

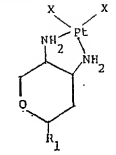


to provide a compound of formula



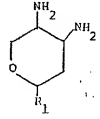
and then reacting that compound with K_2PtX_4;

or (h) a compound of the formula



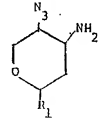
which comprises:

(i) reacting a compound of formula

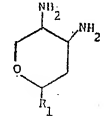


with K_2PtX_4, or

(ii) first catalytically reducing a compound of formula

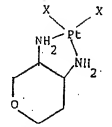


to provide a compound of formula



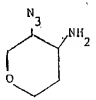
and then reacting that compound with K_2PtX_4;

or (i) a parent compound of the formula

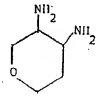


which comprises:
(i) reacting a compound of formula

with K_2PtX_4, or
(ii) first catalytically reducing a compound of formula

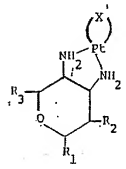


to a compound of formula

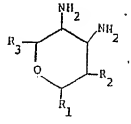


and then reacting that compound with K_2PtX_4;

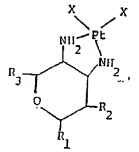
or (j) an analog compound of the formula



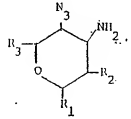
which comprises:
(i) reacting a compound of formula



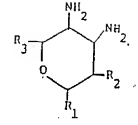
with K_2PtX_4 to provide a compound of formula



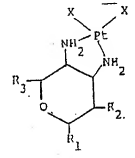
and then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion, X'; or
(ii) first catalytically reducing a compound of formula



to form a compound of formula



then reacting that compound with K_2PtX_4 to provide a compound of formula



and then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion, X';

wherein X is a protective group, R_1 is H, X' is the anion of said di-anionic chelating agent, R_1, H, alkyl or O-alkyl, R_2 is H, OH, alkyl or O-alkyl, and R_3 is H, alkyl, or alkylalkoxy selected from the group consisting of a halogen, e.g., chlorine, bromine, or iodine, a nitrate, sulfate, a monobasic organic acid, e.g. glucuronic acid; a monodentate ligand or a di-anionic chelate group, e.g. oxalates ($C_2O_4$2-), malonates, [$(O_2C)_2CR'R"$] (wherein R' and R" are H, alkyl, OH, or taken together represent alkylene units of 2-3 carbons in length) or 1,1-cyclobutane dicarboxylates.

In accordance with a further aspect, a pharmaceutical composition is provided comprising as the essential active ingredient, a compound selected from those described above, together with a pharmaceutically acceptable carrier therefor.

In accordance with still further aspect of this invention a method is provided for the treatment of tumors comprising: selecting a mammal having such tumor; and treating the mammal with a pharmaceutical composition comprising as the essential active ingredient, a compound as described above, together with a pharmaceutically acceptable carrier therefore.

In the above processes, catalytic reduction may be carried out using conventional techniques and catalysts for that purpose. Such catalysts, temperature conditions and general reaction parameters are known to those skilled in the art.

In addition to the other properties of the compounds of the present invention and as noted above, certain compounds, particularly those in which R_1 is H, or lower alkoxy, R_2 is H, hydroxy or lower alkoxy, and R_3 is hydrogen, have been found to exhibit anti-cancer activity, namely against L1210 leukemia implanted in CDF, mice. The compounds of the present invention have been found to be similar in lab screening profile to the known compound, cisplatin, which places the compounds of this invention in the class of coordination compounds that have therapeutic activity against a wide spectrum of human tumours, either alone or in combination with other agents, e.g. adriamycin, 5-fluorouracil, etc. In 1979, the FDA approved cisplatin for use in humans. Although the mode of action is still unknown, it has been found that cisplatin and its analogs bind to the DNA and disturb the normal functions of the cell. In another hypothesis, the drug is believed to enhance antigenicity so that tumors become more susceptible to destruction by the host's immune system. Moreover, the compounds of the present invention have additional unexpected properties, namely they are more soluble than cisplatin in physiological saline, and they are believed

to be effective against tumors which have a resistance to cisplatin.

Regardless of the precise mode of action, the efficacy and potential of cisplatin as an antitumor agent are of some significance. Although cisplatin exerts its preferential toxicity to tumor cells when compared to normal cells at a therapeutic index which allows its clinical use, the situation is still far from perfect and there are also serious side effects to overcome. An improvement is still sought in therapeutic index. Among the major drawbacks are nephrotoxicity, neurotoxicity, gastro-intestinal problems (emesis) and depression of the function of the bone marrow thus producing fewer than normal white blood cells and platelets. These have obviously limited the size of the dose and continue to be a major impediment to the broader use of cisplatin in humans.

At present, patients using cisplatin are induced to increase their flow of urine by intravenous administration of 1-2 liters of fluid. The drug is then administered intravenously together with a diuretic. A most recent development is the administration of D-mannitol which is believed to "flush out" residual cisplatin from the body. These are nonetheless relatively harsh treatments even in the face of life-threatening situations.

There is a renewed interest in the treatment of a variety of tumors with platinum coordination compounds. (B. Rosenberg, Cancer Treatment Reports 63, 1943 (1979); and Science, 192, 774 (1976); Chem. Eng. News, Jan. 21, 1980, p.35). Reports on the clinical status of cisplatin in cancer chemotherapy, generally on extremely advanced cases, indicate promising anticancer activity. (J.A. Gottlieb and B. Drewinko, Cancer Chemother. Rep., 59, 621 (1975). Cisplatin, as noted

above, has had success in the treatment of testicular carcinoma (H.J. Wallace and D. J. Higby, Recent Results Cancer Res. 48, 167 (1974), hand and neck cancer (I.H. Krakoff and A. J. Lippman, Recent Results Cancer Res., 48, 183 (1974) squamous cell carcinoma, malignant lymphoma and endometrial carcinoma (J. M. Hill et al, Cancer Chemother. Rep., 48, 145 (1974) and J. M. Hill et al, Cancer Chemother. Rep. 59 647 (1975), and ovarian adenocarcinoma (E. Wittshaw and B. Care, Cancer Res., 48, 178 (1974). Researchers at Georgetown University in Washington have reported remarkable success in treating brain tumors with this drug (Chem. Eng. News, Oct. 6, 1980, p. 27). The patients in this case were 10 children whose tumors had resisted many forms of chemotherapy. Even more recent clinical studies are reported as follows:

1. Cisplatin - Current Status and New Developments. AW Preslayko, S.T. Crooke, S.K. Carter (eds), Academic Press, 1980.
2. Platinum Coordination Complexes in Cancer Chemotherapy. M.D. Hacker, E.B. Douple, I.H. Krokoff (eds).
   Developments in Oncology Senes, Martinus Nijhoff, 1984.
3. Platinum Cancer Chemotherapy, Proceedings.
   (M. Nicolini and G. Bandok, (eds), 1987.

As previously mentioned, Cisplatin treatment has certain disadvantages. For example, it is not very soluble in water which renders its intravenous administration questionable. Some derivatives are known to maintain the desired levels of activity (T.A. Connors, M.J. Cleare and K. R. Harrap, Cancer Treatment Reports 63,1499 (1979), but the solubility characteristics were not noticeably improved; thus, e.g. malonato (1,2 diaminocyclohexane) platinum (II) has been found to be effective

against a number of animal tumors in addition to L1210 Leukemia (J.H. Burchenal et al, Cancer Treatment Reports, 63, 1493 (1979). Nephro-toxicity and other forms of toxicity remain as the most serious drawback of cisplatin and the limited number of analogs tested so far. The synthesis of different platinum coordination compounds with greater water solubility, less renal toxicity and greater antitumor activity is a goal that is still actively sought by investigators (see Roberts and Thomson below).

The primary mode of action (J. J. Roberts and A. J. Thomson, Prog. Nucl. Acid Res., Mol. Biol., 22, 71 (1979) and A. D. Kelman and H. J. Persesie, Cancer Treatment Reports, 63, 1445 (1979) of cisplatin and its derivatives is localized at the intracellular DNA level. While the sites within the various bases to which cisplatin binds are known, their relative importance to antitumor activity have not been conclusively discerned. The bound cisplatin drug would result in template inactivation of DNA and the accumulation of potentially lethal damage.

With respect to their transport, again, little is known except that the drug must be able to penetrate the cell membrane prior to exerting intra-cellular tumoricidical action. The active form must be electrically neutral in the plasma prior to transport. Otherwise a carrier-mediated mechanism has to be involved for which there is no evidence (L.A. Zwelling and K. W. Kohn, Cancer Treatment Reports, 63, 1439 (1979).

In the above-defined compounds, the compounds of the present invention exist in one of two positional isomeric forms, as disclosed above. Such compounds also individually exist as stereo-isomers, as will be evident from the Examples hereinafter referred to. Accordingly,

the present invention embraces both the positional isomers and stereo-isomers of the compounds described herein.

Preferred compounds of the present invention are those compounds where R_1, in addition to being H, is lower alkyl, namely alkyl having from 1 to 4 carbon atoms. This likewise applies to the O-alkyl R_1 substituents which preferably have 1 to 4 carbon atoms.

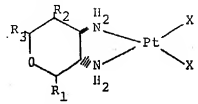
Another series of preferred compounds of the present invention is where R_2, in addition to being H or OH, are compounds where alkyl is lower alkyl, namely alkyl containing from 1 to 4 carbon atoms and as such, this includes O-alkyl as containing 1 to 4 carbon atoms. A particularly preferred group of R_2 substituents is H, OH and lower alkoxy such as methoxy.

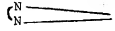
Another series of preferred compounds of the present invention comprises those compounds in which R_3 is H, or lower alkyl, wherein alkyl contains from 1 to 4 carbon atoms; thus, C_1-C_4 alkyl and C_1-C_4 alkyl-O-C_1-C_4 alkyl are preferred groups, with R_3 being most advantageously H.

A most preferred group of compounds of formula II and formula III is where R_1 is H or lower alkoxy, such as methoxy, ethoxy or the like; R_2 is H, OH or lower alkoxy such as methoxy or ethoxy; and R_3 is H or lower alkyl such as methyl or ethyl.

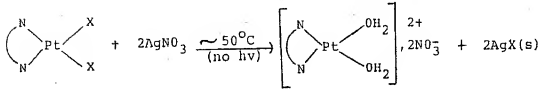
As described before, the protective group X may be any suitable group such as, a halogen, e.g., chlorine, bromine, or iodine, a nitrate, sulfate and a monobasic organic acid such as glucuronic acid; or still further, X can be a monodentate ligand or a di-anionic chelate group, e.g. oxalates ($C_2O_4^{2-}$), malonates, [$(O_2C)_2CR'R"$] (wherein R' and R" are H, alkyl, OH, or taken together represent alkylene units of 2-3 carbons in length) which are typical examples of O,O-bonded chelates or 1,1-cyclobutane dicarboxylates.

Complexes in which the nature of the X group, in the following formula

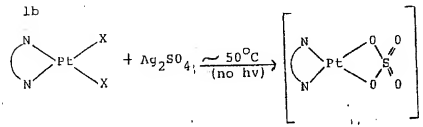


is varied, are prepared according to the following reaction schemes 1a, 1b, and 2a, 2b using the complexes in which X in the starting diamine is I,Cl. The diamine is abbreviated 

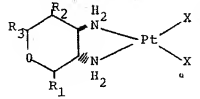
1a

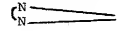


1b

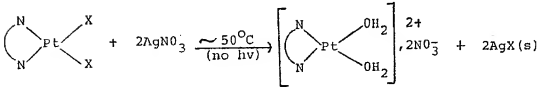


Complexes in which the nature of the X group, in the following formula

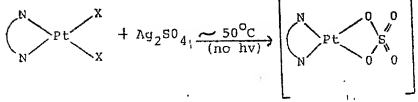


is varied, are prepared according to the following reaction schemes 1a, 1b, and 2a, 2b using the complexes in which X in the starting diamine is I,Cl. The diamine is abbreviated 

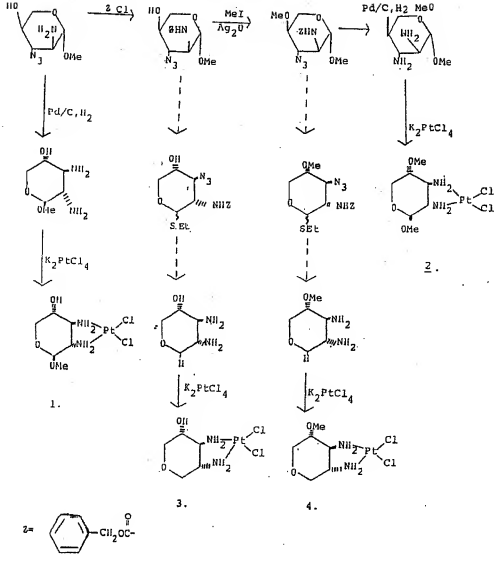
1a



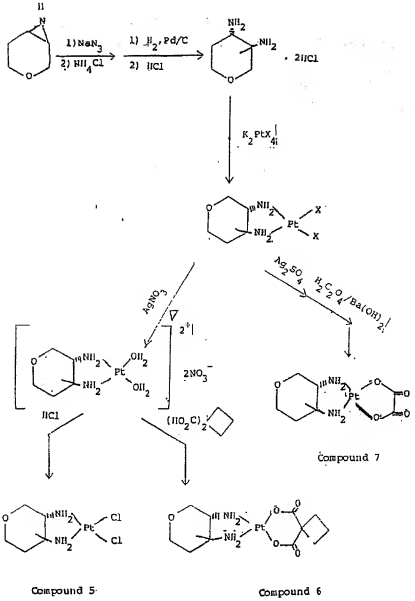
1b



SCHEME



SCHEME



As noted above, one aspect of the invention includes novel compositions of matter and a method of treating certain cancers in mammals using the novel compounds of this invention. The inter-relationship of dosages for animals of various sizes and species and humans is described by Freiereich, E.J., et al., Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey and Man. Cancer Chemother. Rep., 50, No. 4, 219-244, May 1966. A preferred dosage regimen is about 5 mg/day to about 200mg/day, per kg of body weight. This dosage may be adjusted to provide the optimum therapeutic response, and may be administered daily or be proportionally reduced as indicated by the exigencies of the therapeutic situation. The active compound may be administered by the intravenous, intramuscular or subcutaneous routes.

The active compounds may be administered parenterally. Solutions or dispersions of the active compound can be prepared in water, suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Under ordinary conditions of storage and use these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid; it must also be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol, liquid polyethylene

glycol), suitable mixtures thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

As used herein "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subject to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The requisite for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 2 mg to over 200 mg with from about 5 to 180 mg being preferred. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

Regression and palliation of cancers are attained, for example, using intraperitoneal administration. A single intravenous dosage or repeated daily dosages can be administered. Daily dosages up to about 5 to 10 days are often sufficient. It is also possible to dispense one daily dosage or one dose on alternate of less frequent days. As can be seen from the dosage regimens, the amount of principal active ingredient administered is a sufficient amount to aid regression and palliation of the cancer or the like.

Having thus generally described the invention, reference will now be made to the following Examples, describing preferred embodiments.

EXAMPLES

In the following tables and discussion, seven especially preferred compounds of this invention are referred to: compound (1), [SP-4-2(3α,4β,5α,6β)]-dichloro-[4,5-diamino tetrahydro-6-methoxy-2H-pyran-3-ol-N,N'] platinum; compound (2), [SP-4-2-(2β,3α,4β,5α)]-dichloro [tetrahydro-2,5-dimethoxy-2H-pyran-3,4-diamine-N,N'] platinum; compound (3), [SP-4-2-(3α,4β,5α)]-dichloro[4,5-diaminotetrahydro-2H-pyran-3-ol-N,N'] platinum; compound (4), [SP-4-2-(3α,4β,5α)]-dichloro[tetrahydro-5-methoxy-2H-pyran-3,4-diamine-N,N'] platinum; compound (5), [SP-4-2(trans)]-dichloro(tetrahydro-2H-pyran-3,4-diamine-N,N')

platinum; compound (6), [SP-4-2-(trans)]-(ethanedioato(2-)-0,0')-(tetrahydro-2H-pyran-3,4-diamine-N,N') platinum; and compound (7) [SP-4-2-(trans)]-(1,1-cyclobutanedi-carboxylato (2-)O,O^1)(tetrahydro-2H-pyran-3,4-diamine-N,N') platinum.

(1)	128691	[SP-4-2(3α,4β,5α,6β)]-Dichloro-[4,5-diamino tetrahydro-6-methoxy-2H-pyran-3-ol-N,N'] platinum
(2)	128693	[SP-4-2-(2β,3α,4β,5α)]-Dichloro[tetrahydro-2,5-dimethoxy-2H-pyran-3,4-diamine-N,N'] platinum
(3)	-	[SP-4-2-(3α,4β,5α)]-Dichloro[4,5-diaminotetra-hydro-2H-pyran-3-ol-N,N'] platinum
(4)	-	[SP-4-2-(3α,4β,5α)]-Dichloro[tetrahydro-5-methoxy-2H-pyran-3,4-diamine-N,N'] platinum
(5)	130349	[SP-4-2(trans)]-Dichloro(tetrahydro-2H-pyran-3,4-Diamine-N,N') platinum
(6)	130350	[SP-4-2(trans)](Ethane-dioato(2-)-O,O')-(tetra-hydro-2H-pyran-3,4-Diamine-N,N') platinum
(7)	22124X124	[SP-4-2-(trans)]-(1,1-Cyclobutanedi-carboxylato (2-)-O,O')(tetrahydro-2H-pyran-3,4-diamine-N,N') platinum
(8)	1090050	is cisplatin (Diaminedichloro-platinum (II))
(9)	118996	is [SP-4-2]-Dichloro-[1R,2R-Diaminocyclohexane] platinum
(10)	55263	is chlorambucil

Compounds 109050, 118996 and 55263 are included for purposes of comparison.

The results of in vitro tests against various strains of cells L1210 and P388 on separate dates are shown below in Table I.

TABLE 1

ID 50 (g/ml)

Strain	COMPOUND 109050	118996	128691	128693	130349	22124X124	55263
L1210 S	0.283	0.078	4.51	12	1.96	6.6	1.32
L1210 S#	0.258	0.098	3.99	8.92			
L1210 PTR4	2.21	0.09	4.52	5.12	10	45	3.76
L1210 PTR4#	3.43	0.107	4.51	28.4			
DDP5	5.61	0.133	28.2	62.8	12.3	47	3.84
DDP5#	4.19	0.121	17.9	32.2			
L1210/DACH	0.221	1.4	5.69	8.29	11.9	26	1.14
L1210/DACH#	0.534	2.54	13.4	19.5			
P388 S	0.09	0.066	0.973	7	2.01	6.3	0.378
P388 S#	<0.78	0.064	0.995	>3.12			
P388 PTR4	2.68	<1.25	19	64.7	>38	89	1.09
P388 PTR4#	5.05	0.747	15.1	52.1			

Note: # indicates the second set of tests, in both sets of tests 128691, and 128693 were dissolved in saline, while 55263 was dissolved in ethanol.

In vivo testing against intraperitoneol L1210 implants (the results of which are shown in Table II) showed that 128691 was highly active while 128693 although less active also showed marked activity.

ANTITUMOR DATA (in vivo)[a]

TABLE II

Compound	Animal Dose (mg/kg)	Weight Toxicity (#dead/group)	T/C Change,g.	LAD, Activity (%)	Activity Rating	LAD, Activity Rating
128691	50	0/6	-2.7	323	++++	25(++++) LDT
128693	50	1/6	-2.5	218	+++	25(-)
Cis-platin	10	1/6	-4.8	323	++++	
(Control)	5.8	0/6	-0.4	262	++++	

a Dose Schedule: compounds administered (i.p) on Days 3, 7, 11

Tumor: implanted i.p.

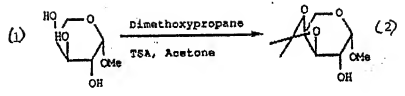
LAD: lowest active dose

LDT: lowest dose tested

These tests demonstrate the anti-cancer properties of the compounds 128691 and 128693.

EXAMPLE 1

(1)

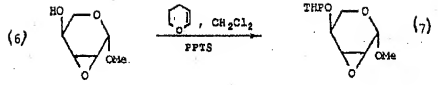


To a solution of dimethoxypropane (3 mMol), p-toluenesulfonic acid monohydrate (0.02 mMol) and acetone (2ml) was added methyl β-L-arabinopyranoside (1) (1 mMol). The mixture was stirred for 1 hour at room temperature. After cooling, the mixture was neutralized with triethylamine, then evaporated below 30°C. The residue was extracted with CH_2Cl_2. The extract was washed with cold water and saturated sodium chloride, dried (Na_2SO_4), evaporated to give a syrup which contained more than 95% of compound (2) methyl 3,4-O-isopropylidene-β-L-arabinopyranoside $[\alpha]_D$ + 192.4 (C 1.81, $CHCl_3$).

lit: a) $[\alpha]_D$ + 199.1 (C 3.3, $CHCl_3$) (Honeyman)
b) $[\alpha]_D$ + 175.7 (C 5.2, $CHCl_3$) (Mukherjee)

NMR, IR spectra confirmed the proposed structure

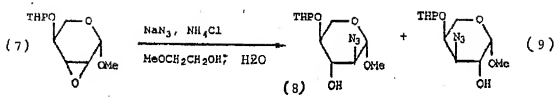
EXAMPLE 2



A solution of the above compound (6) methyl 2,3-anhydro-ß-L-lyxopyranoside obtained from compound (2) methyl-3,4-0-isopropylidene-ß-L-arabinopyranoside via the sequence a) tosylation b) aquacetic acid c) sodium methoxide (0.923 g, 6.32 mMol) and dihydropyran (3 ml, 32.9 mMol) in dry methylene chloride (50 ml) containing pyridinium p-toluenesulfonate (PPTS) (0.18 g, 0.72 mMol) was stirred for 1.5 h at room temperature. The solution was diluted with 50 ml ether, then washed with half-saturated NaCl (2 x 25 ml), dried with anhydrous Na_2SO_4, and evaporated to give a syrup. The syrup was applied to a silica gel column. Elution with ethyl acetate/hexane (1:1) then concentration gave the THP epoxide compound (7) methyl 2,3-anhydro-4-0-tetrahydropyranyl-ß-L-lyxopyranoside (1.32 g, 91%) as a syrup. $[\alpha]_D$ + 65.8 (C 1.23, $CHCl_3$)

NMR, IR spectra confirmed the proposed structure.

EXAMPLE 3



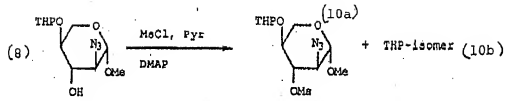
To a solution of the epoxide (7) methyl 2,3-anhydro-4-O-tetrahydropyranyl-β-L-lyxopyranoside of Example 2 (26.4 g, 115 mMol) in 2-methoxyethanol-water (14:1, 1350 ml) was added sodium azide (30 g, 153 mMol) and ammonium chloride (12.3 g, 230 mMol). The mixture was heated at 110°C for 20 hours, and evaporated to give a residue which was extracted with dichloromethane. The extract was washed with water, dried, and evaporated to give a syrup which was applied to a silica gel column. Elution with hexane/ethyl acetate (1:1) gave the THP ether isomers of the above 2-azide derivative (8) methyl 2-azido-2-dioxy-4-O-tetrahydropyranyl-β-L-xylopyranoside-side (7.5 g, 24%).

$[\alpha]_D$ + 11.9 (C 0.78, $CHCl_3$); m.p. 66-68°C, and the THP ether isomers of 3-azide derivative (9) methyl 3-azido-3-dioxy-4-O-tetrahydropyranyl-β-L-arabinopyranoside (14.8 g, 47.2%).

$[\alpha]_D$ + 189.7 (C 1.3, $CHCl_3$)

NMR, IR spectra confirmed the proposed structure.

EXAMPLE 4



To a cold solution of the compound (8) methyl 2-azido-2-dioxy-4-O-tetrahydropoyranyl-β-L-xylopyranoside, Example 3 (7.4 g, 27.1 mMol), pyridine (40 ml) and DMAP (cat.) was added drop-wise a pre-cooled (0°C) solution of methanesulphonyl chloride (6.5 ml, 84 mMol) in 40 ml pyridine. The mixture was left at room temperature for 1 day. After hydrolysis of the excess of methanesulphonyl chloride, the solution was poured into ice-water and extracted with chloroform. The extract was washed with cold hydrochloric acid (2%) and cold water and then dried (Na_2SO_4) and evaporated to give a syrup. Flash column chromatography with ethyl acetate/hexane (1:3, then 2:3, then 1:1) gave the THP isomer 10a (4.09 g, 43%),

$[\alpha]_D$ -26.9 (C 0.85, $CHCl_3$)

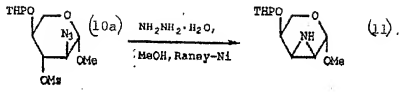
m.p. 89-91°C,

and the THP isomer 10b (3.6 g, 38%)

$[\alpha]_D$ +82.7 (C 1.8, $CHCl_3$)

NMR, IR spectra confirmed the proposed structure.

EXAMPLE 5

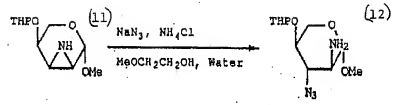


The compound (10a) methyl 2-azido-2-dioxy-3-O-methanesulfonyl-4-O-tetrahydropyranyl-ß-L-xylopyranoside (3 g, 8.55 mMol) in methanol (100 ml) was treated with hydrazine mono-hydrate (99-100%) (4.6 ml, 82.5 mMol). Raney nickel (0.4 g) was added and the mixture boiled under reflux until decomposition of the hydrazine was complete (monitored by TLC, -5h). The mixture was filtered, evaporated to a syrup, then applied to a silica gel column. Elution with AcOEt, then AcOEt-MeOH (10:1) gave compound (11) methyl 2,3-epimino-2,3-dideoxy-4-O-tetrahydropyranyl-ß-L-ribopyranoside (1.9 g, 97%) as a syrup.

$[\alpha]_D$ -80.5 (C 1.11, $CHCl_3$)

IR, MS spectra confirmed the proposed structure.

EXAMPLE 6

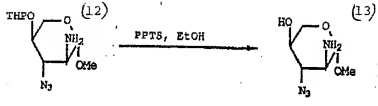


A suspension of the above aziridine compound (11) methyl 2,3-epimino-2,3-dideoxy-4-O-tetrahydropyranyl-β-L-ribopyranoside (1.8 g, 7.86 mMol), sodium azide (2.0 g, 30.77 mMol), and ammonium chloride (0.85 g, 15.89 mMol) in 2-methoxyethanol (112 ml) - water (8 ml) was heated for 11 h at 110°C. The mixture was evaporated directly and the residue extracted with dichloromethane (3 x 100 ml). The extract was washed with half-saturated $NaHCO_3$ (3 x 50 ml), dried (Na_2SO_4) and evaporated to give a yellow syrup which was applied to a silica gel column. Elution with CH_2Cl_2 - MeOH (20:1) gave the compound (12) methyl 2-amino-3-azido-2,3-dideoxy-4-O-tetrahydropyranyl-β-L-xylopyranoside (1.7 g, 80%) as a syrup.

$[\alpha]_D$ -67.9 (C 0.99, $CHCl_3$)

IR, MS, NMR spectra confirmed the proposed structure.

EXAMPLE 7

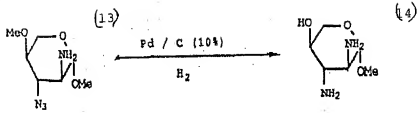


To a solution of THP ether compound (12) methyl 2-amino-3-azido-2,3-dideoxy-4-O-tetrahydropyranyl-β-L-xylopyranoside (32 mg, 0.118 mMol) in ethanol (1.5 ml) was added pyridinium p-toluenesulfonate (PPTS) (59 mg, 0.24 mMol). The solution was stirred for 1 day at 70°C, then evaporated. The residue was applied to a silica gel column. Elution with CH_2Cl_2 - MeOH - triethylamine (100:10:1) followed by concentration, gave compound (13) methyl 2-amino-3-azido-2,3-dideoxy-β-L-xylopyranoside (18 mg, 80%) as crystals.

$[\alpha]_D$ +20.0 (C 0.24, CH_3CH_2OH)
m.p. 141-143°C

IR, MS, NMR spectra confirmed the proposed structure.

EXAMPLE 8

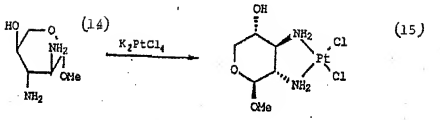


To a solution of the azide (13) methyl 2-amino-3-azido-2,3-dideoxy-β-L-xylopyranoside (395 mg, 2.1 mMol) in methanol-distilled water (1:1, 18 ml) was added palladium-on-activated-charcoal (10% pd, 230 mg) suspended in methanol (3.8 ml). The mixture was hydrogenated under atmospheric pressure at room temperature for 24 hours. The catalyst was then removed by filtration through celite. Evaporation and co-evaporation with ethanol to dryness gave the compound (14) methyl 2,3-diamino-2,3-dideoxy-β-L-xylopyranoside (290 mg, 85%) as white crystals.

$[\alpha]_D$ +84.5 (C 0.33, CH_3OH)
m.p. 200-202°C (decomposition)

NMR, IR spectra confirmed the proposed structure.

EXAMPLE 9



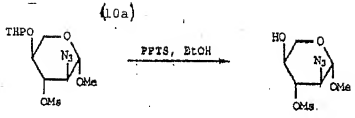
The diamine compound (14) methyl 2,3-diamino-2,3-dideoxy-β-L-xylopyranoside (281 mg, 1 mMol) was transferred, using distilled water (0.9 ml) into a solution containing K_2PtCl_4 (430 mg, 1.03 mMol) in distilled water (3.9 ml). The mixture was stirred manually until homogeneous, and was left standing in darkness. After 2 hours the slow crystallization process began in the form of bright yellow plates. When the original red colour of the solution became yellow or orange-yellow, the crystals were filtered, washed with cold water (3 times) and dried under a stream of air, in the absence of light, for several hours, to afford bright yellow crystals of the compound (15) [SP-4-2-(3α,4β,5α)]-Dichloro[4,5-diaminotetrahydro-2H-pyran-3-ol-N,N']platinum (325 mg, 43.7%).

m.p. 270°C (darkening), 305-310 (decomposition)

$[\alpha]_D$ +144 (C 0.06, H_2O)

MS spectrum confirmed the proposed structure.

EXAMPLE 10



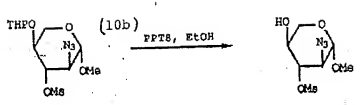
To a solution of THP ether (10a) methyl 2-azido-2-dioxy-3-O-methanesulfonyl-4-O-tetrahydropyranyl-ß-L-xylopyranoside (0.96 g, 2.74 mMol) in ethanol (35 ml) was added pyridinium p-toluenesulfonate (PPTS) (0.1 g, 0.4 mMol). The solution was stirred for 7 hours at 55°C, and then evaporated. The residue was applied to a silica gel column. Elution with hexane/ethyl acetate (4:5, then 1:2) and then concentration gave the compound (16) methyl 2-azido-2-dioxy-3-O-methanesulfonyl-ß-L-xylo-pyranoside (0.73 g. quantitative) as white crystals.

m.p. 111°C-111.5°C

$[\alpha]_D$ +27.0 (C 1.05, $CHCl_3$)

NMR, IR, MS spectra confirmed the proposed structure.

EXAMPLE 11



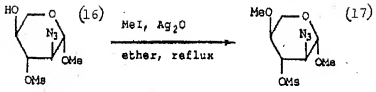
(16)

To a solution of THP ether (10b) which is a diasteromer of (10a) methyl 2-azido-2-dioxy-3-0-methanesulfonyl-4-0-tetrahydroxypyranyl-ß-L-xylo-pyranoside (3.6 g. 10.3 mMol) in ethanol (120 ml) was added pyridinium p-toluenesulfonate (PPTS) (0.5 g, 2 mMol). The solution was stirred for 7 hours at 55°C, and then evaporated. The residue was applied to a silica gel column. Elution with hexane/ethyl acetate (2:3, then 1:3) followed by concentration gave the compound (16) methyl 2-azido-2-dioxy-3-0-methane-sulfonyl-ß-L-xylopyranoside (2.74 g quantitative) as white crystals.

m.p. 110-110°C

$[\alpha]_D$ + 27.3 (C 1.03, $CHCl_3$).

EXAMPLE 12

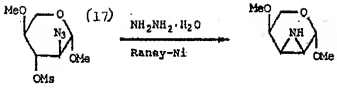


To a solution of compound (16) methyl 2-azido-2-dioxy-3-0-methanesulfonyl-β-L-xylopyranoside (2.48 g., 9.3 mMol) in dry ether (300 ml) was added iodomethane (2.3 ml, 37 mMol), and then dry, finely divided silver oxide (4.3 g, 18.5 mMol) is added in portions. The suspension was heated under reflux for 4 days. After cooling, the mixture was filtered, and evaporated to a syrup which was applied to a silica gel column. Elution with hexane/ethyl acetate (1:1) followed by concentration gave compound (17) methyl 2-azido-dioxy-3,4-di-0-methanesulfonyl-β-L-arabinopyranoside (2.34 g, 89.6%) as a colorless syrup.

$[\alpha]_D$ +34.4 (C 1.51, $CHCl_3$)

NMR and IR spectra confirmed the proposed structure.

EXAMPLE 13

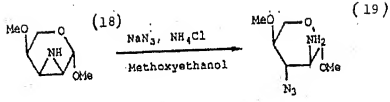


The compound (17) methyl 2-azido-2-dioxy-3,4-0-di-0-methansulfonyl-ß-L-arabinopyranoside (2.29 g, 8.15 mMol) in methanol (100 ml) was treated with hydrazine monohydrate (99-100%) (5.5 ml) and Raney nickel (0.3 g). The mixture was boiled under reflux until decomposition of the hydrazine was complete (monitored by TLC, approximately 5 hours), and then was filtered and evaporated to a syrup which was applied to a silica gel column. Elution with CH_2Cl_2 - MeOH (20:1), followed by concentration gave the aziridine (18) methyl 2,3-epimino-2-3-dideoxy-4-0-methyl-ß-L-ribopyranoside (0.9 g, 70%) as a syrup.

$[\alpha]_D$ -19.9 (C 1.18, $CHCl_3$)

MS, IR spectra confirm the proposed structure.

EXAMPLE 14

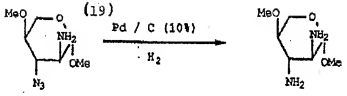


A mixture of the aziridine compound (18) methyl 2,3-epimino-2-3,dideoxy-4-0-methyl-β-L-ribopyranoside (0.84 g, 5.28 mMol), sodium azide (1.4 g, 21.4 mMol) and ammonium chloride (0.58 g, 10.8 mMol) in 2-methoxyethanol (75 ml) - water (5.5 ml) was heated for 17 hours at 110°C, and then evaporated directly. The residue was extracted with dichloromethane (4 x 25 ml) and the resulting solution was washed with half-saturated $NaHCO_3$ (2 x 25 ml), dried (Na_2SO_4), and evaporated to give a syrup which was applied to a silica gel column. Elution with CH_2Cl_2-MeOH (20:1) followed by concentration gave the azide (19) methyl 2-amino-3-azido-2,3-dideoxy-4-0-methyl-β-L-xylo-pyranoside (0.85 g, 80%) as a syrup.

$[\alpha]_D$ -5.2 (C 1.02, $CHCl_3$)

NMR, MS spectra confirmed the proposed structure.

EXAMPLE 15



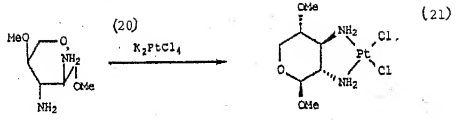
To a solution of the azide (19) methyl 2-amino-3-azido-2,3-dideoxy-4-O-methyl-β-L-xylopyranoside (0.77 g, 3.18 mMol) in methanol-distilled water (1:1, 30 ml) was added palladium-on-activated-charcoal (10% Pd, 400 mg) suspended in methanol (8 ml). The mixture was hydrogenated under atmospheric pressure at room temperature for 24 hours. The catalyst was then removed by filtration through celite*. Evaporation of the resulting solution, followed by co-evaporation with ethanol to dryness gave compound (20) methyl 2,3-diamino-2,3-dideoxy-4-O-methyl-β-L-xylopyranoside (0.63 g, 94%) as white crystals.

$[\alpha]_D$ +101.2 (C 0.60, CH_3OH)
m.p. 60-62°C

NMR, MS spectra confirmed the proposed structure.

* = Trade Mark

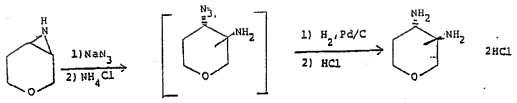
EXAMPLE 16



The diamine (20) methyl 2,3-diamino-2,3-dideoxy-4-O-methyl-β-L-xylopyranoside (0.59 g, 3.35 mMol) was transferred, using distilled water (2.4 ml), into a solution containing K_2PtCl_4 (1.4 g, 3.37 mMol) in distilled water (15 ml). The mixture was stirred manually until homogeneous, and was left standing in darkness. After 4 hours the slow crystallization process began in the form of bright yellow plates. When the original red colour of the solution became yellow or orange-yellow, the crystals were filtered, washed with cold water (5 x 4 ml) and dried under a stream of air in the absence of light, for several hours, to afford bright yellow crystals of (21) [SP-4-2-(3α,4β,5α)]-Dichloro[tetrahydro-5-methoxy-2H-pyran-3,4-diamine-N,N']platinum (0.89 g, 60%).

m.p. 295°C (darkening): 325-330°C (decomposition)
$[\alpha]_D$ +120.9 (C 0.11, H_2).

EXAMPLE 17

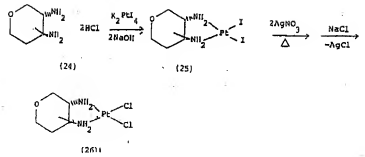


(22) (23) (24)

To 0.6g of(22)96.06 mmol) in 26 ml of EtOH and 8 ml H_2O was added 1.58g of NaN_3 (24 mmol) and 1.30g of NH_4Cl(24mmol). The resulting mixture was refluxed for 1 hour, cooled, and concentrated. The residue was dissolved in H_2O and then extracted continuously with Et_2O for 24 hours. The Et_2O layer was dried and concentrated to yield 1 g of (23). Compound (23) was dissolved in EtOH and hydrogenated at atmospheric pressure (0.15g 10% Pd/C). The resulting solution was filtered through celite and filtrate was acidified with EtOH/HCl to give, after cooling, 0.62g of (24) (54%). Analyses (C,H,N,Cl) were within 0.4% of the theoretical values.

Mass spectroscopic (FAB) and IR analyses confirmed the proposed structure.

EXAMPLE 18

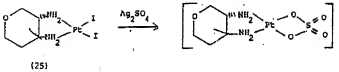


(24) (25) (26)

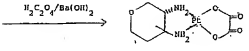
K_2PtI_4 was prepared in situ by adding solid KI (9.4g; 56.6 mmoles) to 95 ml of a solution of K_2PtCl_4 (3.91 g; 9.42 mmoles). To this solution was added, as a solid, the dihydrochloride of compound (24) (A.2HCl) followed by the slow addition of 18.8ml of 1.0N NaOH. The resulting complex (25) was filtered and washed with 0.01N KI and H_2O(0°C). To a 50ml slurry of (25) was added, with stirring, a 50ml solution of $AgNO_3$(3.20g; 18.84 mmoles) to prepare a solution of the corresponding diaquo species, $[PtA(H_2O)_2]^{2+}, 2NO_3^-$. After removal of excess Ag^+ ion using NaCl, 20 ml of 2M NaCl solution was added to the solution of $[PtA(H_2O)_2]^{2+}, 2NO_3^-$ with warming in preparing compound (26), [Pt(3,4-diaminopyran)Cl_2], as a fine yellow powder.

NMR(^{13}C,^1H) and IR confirmed the proposed structure.

EXAMPLE 19



(25)



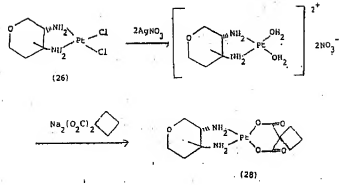
(27)

A solution of Ag_2SO_4 (0.697g; 0.312 mmol) was added to a 10ml(H_2O) slurry of (25), the mixture was warmed (50°C) for 15 minutes, and then allowed to react overnight with agitation. After filtering of AgI(s), the filtrate was treated successively with (1) 15ml of a solution of $H_2C_2O_4$ (0.297g; 2.35 mmol) and (2) 10.25ml of 0.459N $Ba(OH)_2$ solution which was added drop-wise with stirring. After stirring the reaction mixture overnight, the solution (pH = 4.4) was warmed to 55-60°C for 15 minutes, concentrated using a rotoevaporator, and then cooled to 0°C to initiate crystallization. The crystals were collected by filtration, washed thoroughly with H_2O(0°C), 95%EtOH(0°C), and then dried in air and high vacuum. The crude product was re-crystallized from H_2O (0.52g/15mlH_2O @85°C) to yield 0.31g (33%) of (27).

NMR('H,^{13}C), Mass spectroscopy (FAB),

IR confirmed the proposed structure.

EXAMPLE 20



(26)

(28)

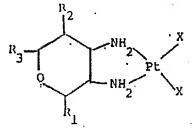
A solution of $AgNO_3$ (1.019g; 6.00 mmole) was added to a stirred slurry of (26) in H_2O. The mixture was warmed for 20 minutes at 50-55°C, and then allowed to react overnight with agitation. After filtering the AgCl(s) formed a solution of $Na_2[(O_2C)_2$◇$]$ (2NaOH + $(HO_2C)_2$◇) was added to the filtrate and the solution was warmed at 50°C for 15 minutes. Cooling to 0°C initiated crystallization. The mixture was placed in a refrigerator, (0°C) overnight. The white crystalline product (28) was filtered, washed (3X) with H_2O(0°C) and absolute EtOH(0°C) and dried in vacuo to constant weight to yield 0.80g(59%) of (28).

NMR(^{13}C, ^{195}Pt), mass (FAB) and IR spectroscopic analysis confirmed the proposed structure.

CLAIMS

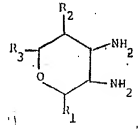
1. A process of preparing:

(a) a compound of the formula



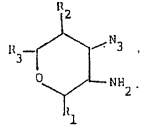
which comprises:

(i) reacting a compound of formula

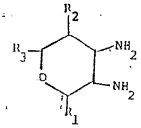


with K_2PtX_4, or

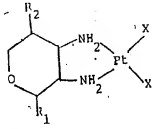
ii) first catalytically reducing a compound of formula



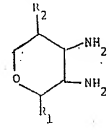
to form a compound of formula



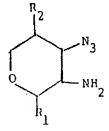
and then reacting that compound with K_2PtX_4;
or (b) a compound of the formula



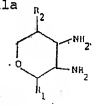
which comprises
(i) reacting a compound of formula



with K_2PtX_4, or
(ii) first catalytically reducing a compound of formula

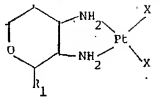


to provide a compound of formula



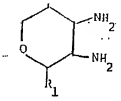
and then reacting that compound with K_2PtX_4;

or (c) a compound of the formula



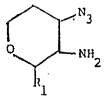
which comprises:

(i) reacting a compound of formula

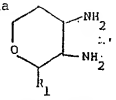


with K_2PtX_4, or

(ii) first catalytically reducing a compound of formula

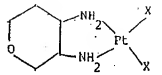


to provide a compound of formula



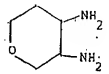
and then reacting that compound with K_2PtX_4;

or (d) a parent compound of the formula



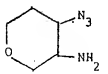
which comprises:

(i) reacting a compound of formula

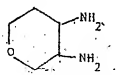


with K_2PtX_4, or

(ii) first catalytically reducing a compound of formula

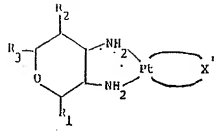


to a compound of formula



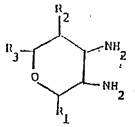
and then reacting that compound with K_2PtX_4;

or (e) an analog compound of the formula

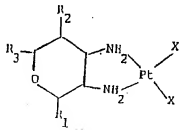


which comprises:

(i) reacting a compound of formula

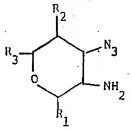


with K_2PtX_4 to provide a compound of formula

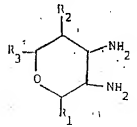


then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion, X'; or

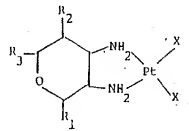
(ii) first catalytically reducing a compound of formula



to form a compound of formula

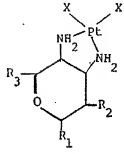


then reacting that compound with K_2PtX_4 to provide a compound of formula



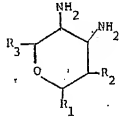
and then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion, X';

or f) a compound of the formula



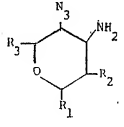
which comprises:

(i) reacting a compound of formula

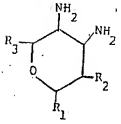


with K_2PtX_4, or

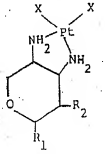
(ii) first catalytically reducing a compound of formula



to form a compound of formula

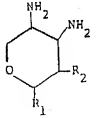


and then reacting that compound with K_2PtX_4; or (g) a compound of the formula



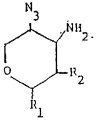
which comprises:

(i) reacting a compound of formula

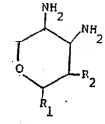


with K_2PtX_4, or

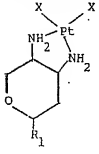
(ii) first catalytically reducing a compound of formula



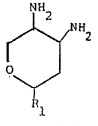
to provide a compound of formula



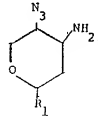
and then reacting that compound with K_2PtX_4;
or (h) a compound of the formula



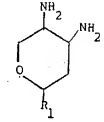
which comprises:
(i) reacting a compound of formula



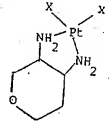
with K_2PtX_4, or
(ii) first catalytically reducing a compound of formula



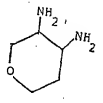
to provide a compound of formula



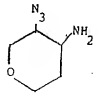
and then reacting that compound with K_2PtX_4;
or (i) a parent compound of the formula



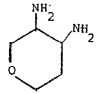
which comprises:
(i) reacting a compound of formula



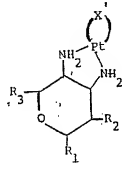
with K_2PtX_4, or
(ii) first catalytically reducing a compound of formula



to a compound of formula

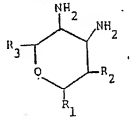


and then reacting that compound with K_2PtX_4; or (j) an analog compound of the formula

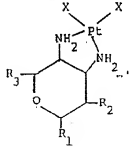


which comprises:

(i) reacting a compound of formula

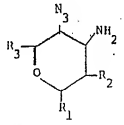


with K_2PtX_4 to provide a compound of formula

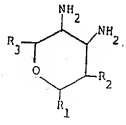


and then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion, X'; or

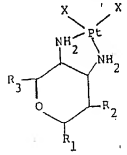
(ii) first catalytically reducing a compound of formula



to form a compound of formula



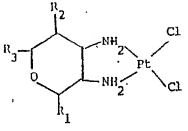
then reacting that compound with K_2PtX_4 to provide a compound of formula



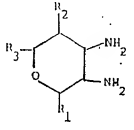
and then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion, X';
wherein X is a protective group, R_1 is H, X' is the anion of said di-anionic chelating agent, R_1, H, alkyl or O-alkyl, R_2 is H, OH, alkyl or O-alkyl, and R_3 is H, alkyl, or alkylalkoxy selected from the group consisting

of a halogen, e.g., chlorine, bromine, or iodine, a nitrate, sulfate, a monobasic organic acid, e.g. glucuronic acid; a monodentate ligand or a di-anionic chelate group, e.g. oxalates ($C_2O_4^{2-}$), malonates, $[(O_2C)_2CR'R"]$ (wherein R' and R" are H, alkyl, OH, or taken together represent alkylene units of 2-3 carbons in length) or 1,1-cyclobutane dicarboxylates.

2. A process as defined in Claim 1 of preparing a compound of the formula

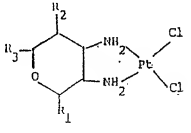


which comprises reacting a compound of formula

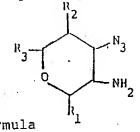


with K_2PtCl_4.

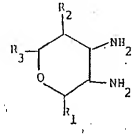
3. A process as defined in Claim 1 of preparing a compound of the formula



which comprises
first catalytically reducing a compound of formula

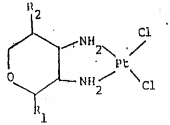


to form a compound of formula

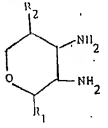


and then reacting that compound with K_2PtCl_4.

4. A process as defined in Claim 1 of preparing a compound of the formula

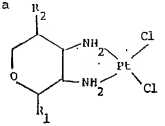


which comprises reacting a compound of formula

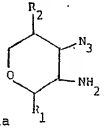


with K_2PtCl_4.

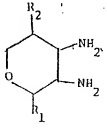
5. A process as defined in Claim 1 of preparing a compound of the formula



which comprises
first catalytically reducing a compound of formula

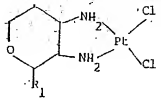


to provide a compound of formula

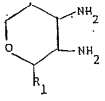


and then reacting that compound with K_2PtCl_4.

6. A process as defined in Claim 1 of preparing a compound of the formula

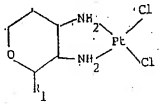


which comprises
(i) reacting a compound of formula

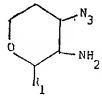


with K_2PtCl_4.

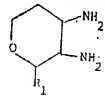
7. A process as defined in Claim 1 of preparing a compound of the formula



which comprises
first catalytically reducing a compound of formula

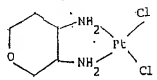


to provide a compound of formula

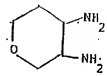


and then reacting that compound with K_2PtCl_4.

8. A process as defined in Claim 1 for preparing a parent compound of the formula

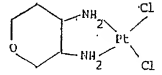


which comprises
reacting a compound of formula

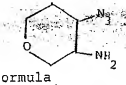


with K_2PtCl_4.

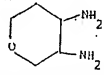
9. A process as defined in Claim 1 for preparing a parent compound of the formula



which comprises
first catalytically reducing a compound of formula

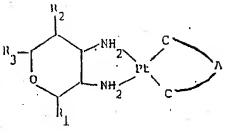


to a compound of formula

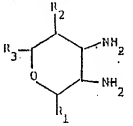


and then reacting that compound with K_2PtCl_4.

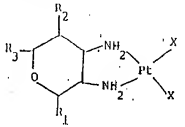
10. A process as defined in Claim 1 for preparing an analog compound of the formula



which comprises
reacting a compound of formula

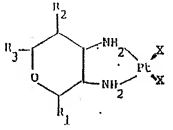


with K_2PtCl_4 to provide a compound of formula

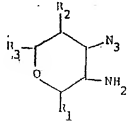


and then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion X', wherein X' is an oxalate, malonate or 1,1-cyclobutanedicarboxylate ion.

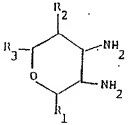
11. A process as defined in Claim 1 for preparing an analog compound of the formula



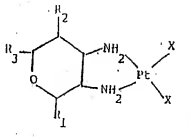
which comprises
first catalytically reducing a compound of formula



to form a compound of formula

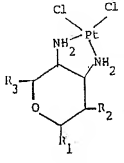


then reacting that compound with K_2PtX_4 to provide a compound of formula

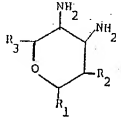


and then reacting that compound with the acid (H_2X) or salt (Na_2X) form of anion X, wherein X is an oxalate, malonate or 1,1-cyclobutanedicarboxylate ion.

12. A process as defined in Claim 1 of preparing a compound of the formula

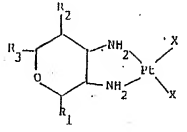


which comprises reacting a compound of formula

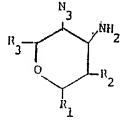


with K_2PtCl_4.

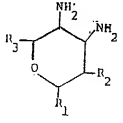
13. A process as defined in Claim 1 of preparing a compound of the formula



which comprises
first catalytically reducing a compound of formula

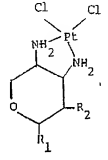


to form a compound of formula

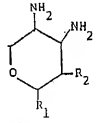


and then reacting that compound with K_2PtCl_4.

14. A process as defined in Claim 1 of preparing a compound of the formula

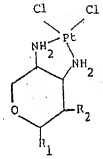


which comprises
reacting a compound of formula

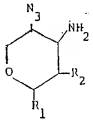


with K_2PtCl_4.

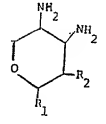
15. A process as defined in Claim 1 of preparing a compound of the formula



which comprises
first catalytically reducing a compound of formula

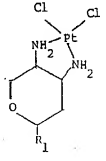


to provide a compound of formula

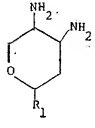


and then reacting that compound with K_2PtCl_4.

16. A process as defined in Claim 1 of preparing a compound of the formula

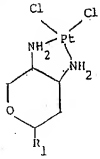


which comprises
reacting a compound of formula

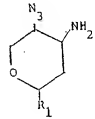


with K_2PtCl_4.

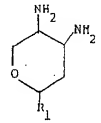
17. A process as defined in Claim 1 of preparing a compound of the formula



which comprises
first catalytically reducing a compound of formula

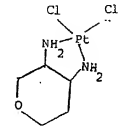


to provide a compound of formula

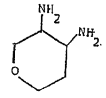


and then reacting that compound with K_2PtCl_4.

18. A process as defined in Claim 1 for preparing a parent compound of the formula

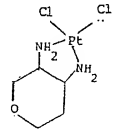


which comprises:
reacting a compound of formula

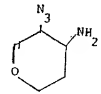


with K_2PtCl_4.

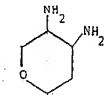
19. A process as defined in Claim 1 for preparing a parent compound of the formula



which comprises
first catalytically reducing a compound of formula

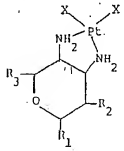


to provide a compound of formula

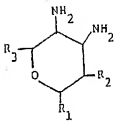


and then reacting that compound with K_2PtCl_4.

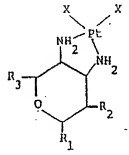
20. A process as defined in Claim 1 for preparing an analog compound of the formula



which comprises
reacting a compound of formula

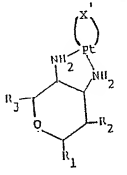


with K_2PtX_4 to provide a compound of formula

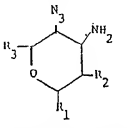


and then reacting that compound with the acid (H_2X) or salt (Na_2X) form of anion X, wherein X is an oxalate, malonate or 1,1-cyclobutanedicarboxylate ion.

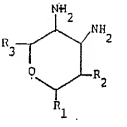
21. A process as defined in Claim 1 for preparing an analog compound of the formula



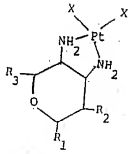
which comprises
first catalytically reducing a compound of formula



to provide a compound of formula

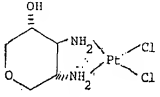


then reacting that compound with K_2PtX_4 to provide a compound of formula

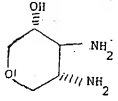


and then reacting that compound with the acid (H_2X') or salt (Na_2X') form of anion, X'; or, wherein X' is an oxalate, malonate or 1,1-cyclobutanedicarboxylate ion.

22. A process of preparing a compound of the formula

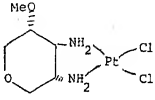


by reacting a compound of the formula

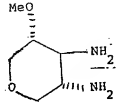


with K_2PtCl_4.

23. A process of preparing a compound of the formula

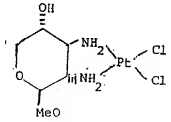


by reacting a compound of formula

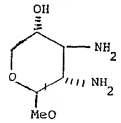


with K_2PtCl_4.

24. A process as defined in Claim 1 of preparing a compound of the formula

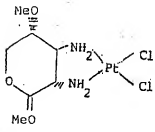


which comprises
reacting a compound of formula

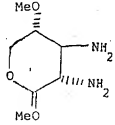


with K_2PtCl_4.

25. A process of preparing a compound of the formula



which comprises
reacting a compound of formula



with K_2PtCl_4.

26. A process as defined in Claim 1 which comprises selecting the starting diamine compound whereby to produce a novel substituted (3,4-diamino-tetrahydropyran dihaloplatinum-(II) complex selected from the group consisting of:

(1) [SP-4-2(3α,4β,5α,6β)]-dichloro-[4,5-diamino tetrahydro-6-methoxy-2H-pyran-3-ol-N,N'] platinum;

(2) [SP-4-2-(2β,3α,4β,5α)]-dichloro[tetrahydro-2,5-dimethoxy-2H-pyran-3,4-diamine-N,N'] platinum;

(3) [SP-4-2-(3α,4β,5α)]-dichloro[4,5-diaminotetra-hydro-2H-pyran-3-ol-N,N'] platinum;

(4) [SP-4-2-(3α,4β,5α)]-dichloro[tetrahydro-5-methoxy-2H-pyran-3,4-diamine-N,N'] platinum;

(5) [SP-4-2(trans)]-dichloro(tetrahydro-2H-pyran-3,4-diamine-N,N') platinum;

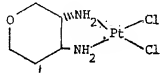
(6) [SP-4-2(trans)](ethanedioato(2-)-O,O')-(tetrahydro-2H-pyran-3,4-diamine-N,N') platinum; and

(7) [SP-4-2-(trans)]-(1,1-cyclobutonedi-carboxylato(2-)-O,O')(tetrahydro-2H-pyran-3,4-diamine-N,N') platinum.

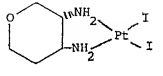
27. A process for the preparation of [SP-4-2(3α, 4β,5α)]- dichloro-[4,5-diaminotetrahydro-2H-pyran-3-ol-N,N'] platinum which comprises reacting methyl 2,3-diamino-2,3-dideoxy-β-L-xylopyranoside with K_2PtCl_4.

28. A process for the preparation of [SP-4-2-(3α, 4β,5α)]-dichloro[tetrahydro-5-methoxy-2H-pyran-3,4-diamine-N,N'] platinum which comprises reacting methyl 2,3-dideoxy-4-0-methyl-β-L-xylopyranoside with K_2PtCl_4.

29. A process for the preparation of

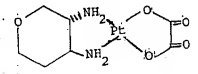


which comprises reacting

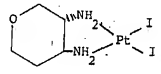


with a solution of silver nitrate, followed by removal of excess silver ions and reaction with a sodium chloride solution.

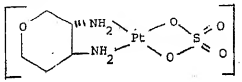
30. A process for preparing



which comprises reacting

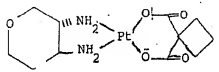


with a solution of silver sulphate, followed by reaction of the intermediate

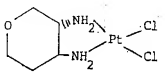


with a solution of oxalic acid and barium hydroxide.

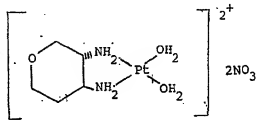
31. A process for preparing



which comprises reacting



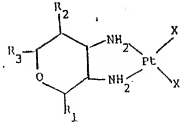
with a solution of silver nitrate,
followed by the reaction of the intermediate



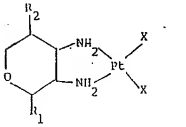
with a solution of sodium malonate.

32. A compound selected from the group consisting of

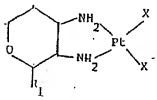
(a)

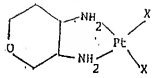


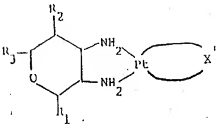
(b)

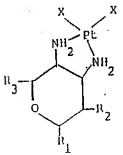


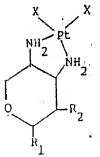
(c)



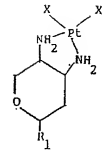
(d) 

(e) 

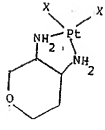
(f) 

(g) 

(h)

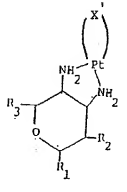


(i)



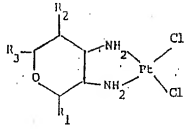
; and

(j)

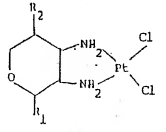


wherein X is a protective group, selected from the group consisting of halides and di-anionic chelating agents, R_1 is H, alkyl or O-alkyl, R2 is H, OH, alkyl or O-alkyl, and R_3 is H, alkyl, or alkylalkoxy.

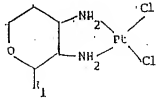
33. A compound as defined in Claim 32 of the formula



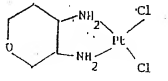
34. A compound as defined in Claim 32 of the formula



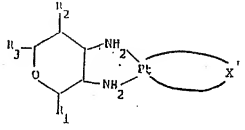
35. A compound as defined in Claim 32 of the formula



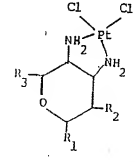
36. A compound as defined in Claim 32 of the formula



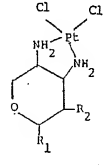
37. A compound as defined in Claim 32 of the formula



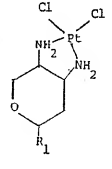
38. A compound as defined in Claim 32 of the formula



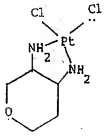
39. A compound as defined in Claim 32 of the formula



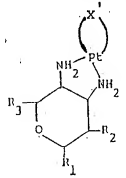
40. A compound as defined in Claim 32 of the formula



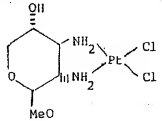
41. A compound as defined in Claim 32 of the formula



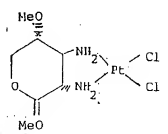
42. A compound as defined in Claim 32 of the formula



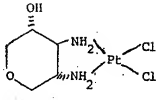
43. A compound of the formula



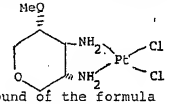
44. A compound of the formula



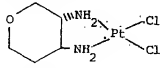
45. A compound of the formula



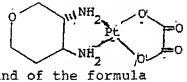
46. A compound of the formula



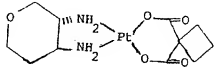
47. A compound of the formula



48. A compound of the formula



49. A compound of the formula



50. A novel substituted (3,4-diaminotetrahydropyran) dihaloplatinum-(II) complex selected from the group consisting of:

(1) [SP-4-2(3α,4β,5α,6β)]-dichloro-[4,5-diamino tetrahydro-6-methoxy-2H-pyran-3-ol-N,N'] platinum;

(2) [SP-4-2-(2β,3α,4β,5α,)]-dichloro[tetrahydro-2,5-dimethoxy-2H-pyran-3,4-diamine-N,N'] platinum;

(3) [SP-4-2-(3α,4β,5α,)]-dichloro[4,5-diaminotetrahydro-2H-pyran-3-ol-N,N'] platinum;

(4) [SP-4-2-(3α,4β,5α,)]-dichloro[tetrahydro-5-methoxy-2H-pyran-3,4-diamine-N,N'] platinum;

(5) [SP-4-2(trans)]-dichloro(tetrahydro-2H-pyran-3,4-diamine-N,N') platinum;

(6) [SP-4-2(trans)](ethanedioato(2-)-O,O')-(tetrahydro-2H-pyran-3,4-diamine-N,N') platinum; and

(7) [SP-4-2-(trans)]-(1,1-cyclobutonedi-carboxylato (2-)-O,O')(tetrahydro-2H-pyran-3,4-diamine-N,N') platinum.

51. A pharmaceutical composition comprising as the essential active ingredient, a compound according to Claim 32, together with a pharmaceutically acceptable carrier therefore.

52. A pharmaceutical composition comprising as the essential active ingredient, a compound according to Claim 50, together with a pharmaceutically acceptable carrier therefore.

53. A method for the treatment of tumors which comprises: selecting a mammal having such tumor; and treating said mammal with a pharmaceutical composition comprising as the essential active ingredient, a compound according to Claim 32, together with a pharmaceutically acceptable carrier therefore.

54. A method for the treatment of tumors which comprises: selecting a mammal having such tumor; and treating said mammal with a pharmaceutical composition comprising as the essential active ingredient, a compound according to Claim 50, together with a pharmaceutically acceptable carrier therefore.

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